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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
COLLINS, CYNTHIA E	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 06/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/701,572	KONDOROSI ET AL.	
	Examiner	Art Unit	
	Cynthia Collins	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,8-15,17,19-28,30 and 32-41* is/are pending in the application.

4a) Of the above claim(s) *1,2 and 8-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,15,19-28,30 and 32-41* is/are rejected.

7)☒ Claim(s) *13,14 and 17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

Applicant's amendment after-final filed on May 2, 2005 has been entered.

The finality of the office action mailed December 2, 2004 is hereby withdrawn.

Claims 3-7, 16, 18, 29 and 31 are cancelled.

Claims 1-2, 8-15, 17, 19-28, 30 and 32-41 are pending.

Claims 1-2 and 8-11 are withdrawn.

Claims 12, 13, 14, 15, 17, 19 and 30 are currently amended.

Claims 12-15, 17, 19-28, 30 and 32-41 are examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

All previous objections and rejections not set forth below have been withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12, 15, 20-28, 40 and 41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to an isolated or purified nucleic acid comprising: (a) a polynucleotide sequence encoding the polypeptide of SEQ ID NO: 2, or (b) a sequence that

hybridizes under stringent conditions to the full-length complement of the coding portion of SEQ ID NO: 1 wherein the coding portion of SEQ ID NO: 1 encodes the full-length CCS52Ms polypeptide of SEQ ID NO: 2, and that encodes a polypeptide that comprises WD-40 repeats and that inhibits mitosis and induces endoreplication, wherein stringent conditions in (b) comprise washing in 0.5X SSC at 65°C. The claims are also drawn to a vector, host cell, plant cell and transgenic plant comprising said nucleic acid. The claims are additionally drawn to the nucleic acid of Claim 12 wherein said sequence encodes a protein comprising amino acid residues 51-55 and 57 of SEQ ID NO: 2 or wherein said sequence encodes a protein comprising amino acid residues 81, 84, 85, 90 and 91 of SEQ ID NO: 2.

The specification describes a single polynucleotide sequence that encodes a polypeptide that inhibits mitosis and induces endoreplication, the purified nucleic acid of SEQ ID NO:1 (ccs52Ms) obtained from *Medicago sativa* that encodes a polypeptide of SEQ ID NO:2 (CCS52Ms). The specification does not describe other polynucleotide sequences that hybridize under stringent conditions to the full-length complement of the coding portion of SEQ ID NO: 1 and that encode a polypeptide that inhibits mitosis and induces endoreplication.

The Federal Circuit has recently clarified the application of the written description requirement to polynucleotide sequences. The court stated that "A description of a genus of cDNAs may be achieved by means of recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial

portion of the genus." See *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1569; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

In the instant case Applicant has not described a representative number of species falling within the scope of the claimed genus which encompasses polynucleotide sequences that hybridize under stringent conditions to the full-length complement of the coding portion of SEQ ID NO: 1 and that encode a polypeptide that inhibits mitosis and induces endoreplication, nor the structural features unique to the genus.

Claims 12, 15, 19-28, 30 and 32-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid comprising SEQ ID NO:1, an isolated nucleic acid encoding SEQ ID NO:2, and an antisense sequence consisting of the 1.2 kb SstI-PvuII fragment of SEQ ID NO: 1 placed in the antisense orientation under the control of a promoter, does not reasonably provide enablement for other polynucleotide sequences, or for polynucleotide sequences encoding other polypeptides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to an isolated or purified nucleic acid comprising: (a) a polynucleotide sequence encoding the polypeptide of SEQ ID NO: 2, or (b) a sequence that hybridizes under stringent conditions to the full-length complement of the coding portion of SEQ ID NO: 1 wherein the coding portion of SEQ ID NO: 1 encodes the full-length CCS52Ms polypeptide of SEQ ID NO: 2, and that encodes a polypeptide that comprises WD-

40 repeats and that inhibits mitosis and induces endoreplication, wherein stringent conditions in (b) comprise washing in 0.5X SSC at 65°C, including a sequence encoding a polypeptide identical to SEQ ID NO: 2 except that residue 16 is G and residue 141 is I. The claims are also drawn to a vector, host cell, plant cell and transgenic plant comprising said nucleic acid. The claims are additionally drawn to a nucleic acid that hybridizes to SEQ ID NO: 1 under stringent conditions, wherein stringent conditions comprise washing in 0.5X SSC at 65°C and which inhibits the expression of the polypeptide of SEO ID NO: 2, which is selected from the group consisting of the full complement of SEO ID NO:1, the full complement of the coding portion of SEQ ID NO: 1, and an antisense sequence consisting of the 1.2 kb SstI-PvuII fragment of SEQ ID NO: 1 when placed in the antisense orientation under the control of a promoter. The claims are further drawn to a vector, host cell, plant cell and transgenic plant comprising said nucleic acid. The claims are also drawn to the nucleic acid of Claim 12 wherein said sequence encodes a protein comprising amino acid residues 51-55 and 57 of SEQ ID NO: 2 or wherein said sequence encodes a protein comprising amino acid residues 81, 84, 85, 90 and 91 of SEQ ID NO: 2.

The specification discloses a single polynucleotide sequence that encodes a polypeptide that inhibits mitosis and induces endoreplication, the purified nucleic acid of SEQ ID NO:1 (ccs52Ms) obtained from *Medicago sativa* that encodes a polypeptide of SEQ ID NO:2 (CCS52Ms). The specification also discloses a single antisense sequence that inhibits the expression of the polypeptide of SEO ID NO: 2, the 1.2 kb SstI-PvuII fragment of SEQ ID NO: 1 when placed in the antisense orientation under the control of a promoter. The specification does not disclose how to make and use other polynucleotide sequences that

hybridize under stringent conditions to the full-length complement of the coding portion of SEQ ID NO: 1 and that encode a polypeptide that inhibits mitosis and induces endoreplication. The specification also does not disclose how to make and use other polynucleotide sequences that inhibit the expression of SEQ ID NO:2.

The full scope of the claimed invention is not enabled because the function of polypeptides encoded by sequences that hybridize under stringent conditions to the full-length complement of the coding portion of SEQ ID NO: 1 is unpredictable, since structurally homologous sequences are not always functionally homologous.

See, for example, Broun P et al. (Catalytic plasticity of fatty acid modification enzymes underlying chemical diversity of plant lipids. Science. 1998 Nov 13;282(5392):1315-7), who teach that a *Lesquerella fendleri* oleate hydroxylase having 81% sequence identity to an *Arabidopsis thaliana* oleate desaturase has only 71 % sequence identity to *Ricinus communis* oleate hydroxylase (page 1315 column 2 first full paragraph). Broun et al. also teach that as few as four amino acid substitutions can change an oleate 12-desaturase to a hydroxylase (paragraph spanning pages 1316-1317).

In the instant case the specification does not provide sufficient guidance with respect to which structural elements of SEQ ID NO:1 would be retained by sequences encoding a polypeptide that inhibits mitosis and induces endoreplication. Absent such guidance one skilled in the art would have to isolate and or synthesize numerous different sequences that hybridize under stringent conditions to the full-length complement of the coding portion of SEQ ID NO: 1, and then test the polypeptide encoded by each sequence for its ability to inhibit mitosis and induce endoreplication in order to discriminate between those sequences

that function as desired and those that do not. Such a trial and error approach to practicing the claimed invention would constitute undue experimentation.

The full scope of the claimed invention is also not enabled because the effect of expressing antisense transcripts in plants is unpredictable, as the ability of a particular antisense transcript to suppress gene expression depends on multiple variables which include but are not limited to the length of the antisense transcript, its position relative to the parent gene, the degree of homology between the antisense transcript and the gene to be suppressed, and the timing, location and level of antisense transcript expression.

See, for example, Sandler S.J. et al. (Inhibition of gene expression in transformed plants by antisense RNA. Plant Molecular Biology, 1988, Vol. 11, No. 3, pages 301-310), who teach that DNA fragments encoding different portions of the nopaline synthase gene, when expressed as antisense transcripts, vary in their ability to inhibit nopaline synthase gene expression (page 308 column 2 and Table 4, page 309 column 1 first full paragraph). Antisense transcripts downstream from the Cla I site (nucleotide 373) effectively suppressed nopaline synthase gene expression, whereas the full length antisense transcript and the antisense transcript upstream from the Cla I site (nucleotides 1 to 373) did not (id).

See also, for example, van der Krol A.R. et al. (Inhibition of flower pigmentation by antisense CHS genes: promoter and minimal sequence requirements for the antisense effect. Plant Mol Biol. 1990 Apr;14(4):457-66), who teach a method of decreasing the expression of an endogenous petunia chalcone synthase gene by transforming petunia cells with chimeric genes comprising chalcone synthase (CHS) coding sequences operably linked in an antisense orientation to a CaMV 35S constitutive promoter. The full length CHS cDNA and CHS

sequences encoding half-length or quarter-length RNA complementary to the 3' half of the CHS mRNA decreased the expression of endogenous CHS, whereas half-length RNA complementary to the 5' half of the CHS mRNA did not (page 460 Figures 1 and 2;page 461 Figure 3).

See additionally, for example, Mizukami Y. et al. (Separation of AG function in floral meristem determinacy from that in reproductive organ identity by expressing antisense AG RNA. Plant Mol Biol. 1995 Aug;28(5):767-84), who teach that transgenic *Arabidopsis* plants carrying an antisense AGAMOUS construct may produce three different types of abnormal flowers depending on the level of reduction of AGAMOUS expression: flowers having floral meristem indeterminacy and floral organ conversion, flowers having floral meristem indeterminacy and partial conversion of all floral organs, and flowers having floral meristem indeterminacy and normal stamens and carpels (pages 770-771 Figure 1; page 775 Figure 4; page 775 Table 1 and Figure 5).

In the instant case the specification does not provide sufficient guidance with respect to how to express antisense transcripts other than the 1.2 kb SstI-PvuII fragment of SEQ ID NO: 1 such that the expression of the polypeptide of SEO ID NO: 2 is inhibited in a useful manner. Absent such guidance one skilled in the art would have to test different conditions for the expression of the full complement of SEQ ID NO:1 and the full complement of the coding portion of SEQ ID NO: 1 in order to determine how to inhibit the expression of the polypeptide of SEO ID NO: 2 in a useful manner. Such a trial and error approach to practicing the claimed invention would constitute undue experimentation.

The full scope of the claimed invention is additionally not enabled because the function of polypeptides in which amino acids have been changed is unpredictable, since a change in as few as one amino acid in a polypeptide can alter or eliminate its function.

See, for example, Rhoads D.M. et al. (Regulation of the cyanide-resistant alternative oxidase of plant mitochondria. Identification of the cysteine residue involved in alpha-keto acid stimulation and intersubunit disulfide bond formation. J Biol Chem. 1998 Nov 13;273(46):30750-6), who teach that mutation of Cys-128 to Ala in an *Arabidopsis* alternative oxidase caused a pronounced overall increase in enzyme activity relative to the wild-type in the presence or absence of pyruvate (page 30753 Figure 3). Mutation of Cys-78 to Ala in the same *Arabidopsis* alternative oxidase resulted in a minimally active enzyme that showed no response to added pyruvate (page 30753 Figure 3).

In the instant case the specification does not provide sufficient guidance with respect to which amino acid changes can be made in a polypeptide of SEQ ID NO:2 such that resultant polypeptide variant still functions to inhibit mitosis and induce endoreplication, or with respect to how to modify variants of SEQ ID NO:2 such that they function to inhibit mitosis and induce endoreplication. Absent such guidance one skilled in the art would have to test and/or modify each polypeptide variant encompassed by the claims in order to determine how to use each variant to inhibit mitosis and induce endoreplication. Such a trial and error approach to practicing the claimed invention would constitute undue experimentation.

With respect to the enablement of the polypeptide variant of claim 19, Applicants point out that the polypeptide of claim 19 differs from the polypeptide of SEQ ID NO:2 by

only two amino acid residues (R16G and V141I), and that these substitutions are unlikely to be involved in the activity of the polypeptide since they are no located in conserved regions. Applicants point out that these substitutions are not located in one of the seven domains with repeated WD40 motifs, and more particularly, not located in the latter domain VII comprising a potential binding site for the mitotic cyclins, degradation of mitotic cyclins by the FZR proteins being necessary to inhibit mitosis and to induce endoreplication. Applicants accordingly submit that the polypeptide of claim 19 is adequately enabled. (reply pages 9-10)

Applicants' argument filed May 2, 2005 has been fully considered but is not persuasive because conserved regions of polypeptides are not necessarily functionally significant, and because nonconserved regions of polypeptides may be functionally significant.

See, for example, Falcon-Perez JM et al. (Functional domain analysis of the yeast ABC transporter Ycf1p by site-directed mutagenesis. J Biol Chem. 1999 Aug 13;274(33):23584-90), who generated twenty-two single amino acid substitutions or deletions by site-directed mutagenesis in the nucleotide binding domains, the proposed regulatory domain, and the fourth cytoplasmic loop, of the yeast cadmium factor (Ycf1p) vacuolar protein. Two conserved amino acid residues, Glu(709) and Asp(821), were found by Falcon-Perez JM et al. to be unnecessary for Ycf1p biogenesis and function.

See also, for example, Lamberg A. et al. (Site-directed mutagenesis of the alpha subunit of human prolyl 4-hydroxylase. Identification of three histidine residues critical for catalytic activity. J Biol Chem. 1995 Apr 28;270(17):9926-31), who teach that mutation of the nonconserved histidine 324 of human prolyl 4-hydroxylase totally prevented tetramer

assembly and eliminated enzyme activity, whereas mutation of the 3 other nonconserved histidines had no effect (page 9927 Figure 1; page 9928 Figure 2 and Table I).

Double Patenting

Claim 13 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 17. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Allowable Subject Matter

Claims 13, 14 and 17 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form.

Remarks

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia Collins whose telephone number is (571) 272-0794. The examiner can normally be reached on Monday-Friday 8:45 AM -5:15 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Cynthia Collins
Examiner
Art Unit 1638

CC

Cynthia Collins 6/11/05